Case Nos. 14-1139, 14-1142, 14-1144

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

ARIOSA DIAGNOSTICS, INC., NATERA, INC., AND VERINATA HEALTH, INC.,
Plaintiffs-Appellees,

AND

DNA DIAGNOSTICS CENTER, INC.,
Counterclaim Defendant-Appellee,

AND

THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY
Plaintiff,

v.

SEQUENOM, INC., AND SEQUENOM CENTER FOR MOLECULAR MEDICINE, LLC
Defendants-Appellants,

AND

ISIS INNOVATION LIMITED,
Defendant.

ON APPEAL FROM THE UNITED STATES DISTRICT COURT FOR THE NORTHERN DISTRICT OF CALIFORNIA IN CASE NOS. 3:11-CV-00132, 3:11-CV-00865, AND 3:11-CV-06391, JUDGE SUSAN ILLSTON

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May 5, 2014

CERTIFICATE OF INTEREST

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1. The full name of every party or amicus represented by us is:

   Ariosa Diagnostics, Inc.

2. The name of the real party in interest represented by us is:

   None

3. All parent corporations and any public companies that own 10 percent or more of the stock of the parties represented by us are:

   None

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3. All parent corporations and any public companies that own 10 percent or more of the stock of the parties represented by us are:

   Formerly known as Artemis Health Inc., Verinata Health, Inc., is a wholly owned subsidiary of Illumina, Inc. Illumina, Inc., is traded under the symbol "ILMN."

4. The names of all law firms and the partners or associates that appeared for the parties now represented by us in the trial court or are expected to appear in this Court are:

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Counsel for Plaintiff/Counterclaim Defendant-Appellee Natera, Inc. certifies as follows:

1. The full name of every party or amicus represented by us is:

   Appellee Natera, Inc. ("Natera")
   Appellee DNA Diagnostics Center, Inc. ("DDC")

2. The name of the real party in interest represented by us is:

   Not applicable.

3. All parent corporations and any public companies that own 10 percent or more of the stock of the parties represented by us are:

   Natera: none.

   DDC: Oaktree Capital Management, a publicly held company, owns 10 percent or more of DDC.

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STATEMENT OF RELATED CASES

Appellant Sequenom, Inc. previously filed an appeal seeking reversal of the District Court's Order denying Sequenom's motion for a preliminary injunction. *Aria Diagnostics, Inc. v. Sequenom, Inc.*, Case No. 12-1531, 726 F.3d 1296 (Fed. Cir. 2013). This Court vacated and remanded the District Court's Order denying Sequenom's motion. In so doing, this Court offered no opinion "as to whether there is or is not a substantial question regarding the subject matter eligibility of the asserted claims" of United States Patent No. 6,258,540 (the "'540 patent"). *Id*. at 1304.

STATEMENT OF THE ISSUES

Whether the claims of the '540 patent are addressed to patent-eligible subject matter where those claims, apart from the natural phenomenon of paternally inherited cell-free DNA of fetal origin in maternal serum or plasma, include no meaningful limitations on the use of the natural phenomenon and involve no more than well-understood, routine, conventional activity, previously engaged in by those in the field; and those steps, when viewed as a whole, add nothing significant beyond the sum of their parts taken separately?

STATEMENT OF THE CASES AND FACTS

Sequenom is one of several participants in the field of non-invasive prenatal testing, a new but rapidly advancing field that also includes Appellees Ariosa

Diagnostics, Inc., Verinata Health, Inc., and Natera, Inc. In 2005, Sequenom obtained an exclusive license to the ’540 patent from Isis Innovation. Br. at 11. The “Summary of the Invention” in the ’540 patent announces that “[i]t has now been discovered that foetal DNA is detectable in maternal serum or plasma samples,” A0039 (1:50-51), and then describes the claimed invention *as that discovery itself*: a method of “detecting the presence of a nucleic acid of foetal origin in the sample,”—*i.e*., detecting the naturally occurring phenomenon of cell-free fetal DNA (“cffDNA”) in maternal serum or plasma. *Id*. (2:1-4). The ’540 patent lists Drs. Yuk-Ming Dennis Lo and James Wainscoat as inventors (sometimes referred to herein as “applicants”). A0034. The earliest application to which the ’540 patent claims priority was filed in March 1997. *Id.*

Since obtaining the rights to the ’540 patent and developing its MaterniT21 test to detect fetal aneuploidy, Sequenom has broadly interpreted the ’540 patent as encompassing ***any*** use of cffDNA and has publicly threatened *anyone* intending to operate in the field of non-invasive prenatal testing of cffDNA in maternal blood with claims of patent infringement. For example, in July 2011, Sequenom staked out its position that “management believes the in-licensed ’540 patent ... will block all non-invasive cell-free DNA-based approaches.” A1225.

Sequenom’s actions have been consistent with that statement. In July 2011, Sequenom disclosed that Verinata would infringe the ’540 patent when Verinata

launched its own non-invasive prenatal test. A1224-25. Sequenom's chairman and CEO later stated that "[w]e believe that [Verinata] would be infringing our 540 patent ... on the use of circulating cell-free fetal nucleic acids." A1006.

Sequenom also directed an attack at Natera and Natera's licensee, DNA Diagnostics Center ("DDC"), after Natera began to offer a non-invasive paternity test in August 2011. A1002-03 (¶ 6). For example, Sequenom told Natera and DDC that "Sequenom holds an exclusive license to patent rights relating to detecting fetal nucleic acids from maternal circulation, and as such, [Natera's] noninvasive paternity test requires a license." *Id*. (¶ 6(b)).

In response to these and other threats, Ariosa filed suit against Sequenom in the Northern District of California on December 19, 2011, seeking a declaration that no activities relating to its Harmony™ Prenatal Test infringe any claim of the '540 patent. A0058 (Dkt. No. 1). Sequenom counterclaimed for infringement,[1] A0061 (Dkt. No. 33), and filed a motion for a preliminary injunction to enjoin Ariosa from allegedly infringing the '540 patent with the Harmony™ Prenatal Test. A0061 (Dkt. No. 34). As one of its affirmative defenses, Ariosa alleged that all asserted claims of the '540 patent are invalid. A0063 (Dkt. No. 52).

[1] Sequenom asserted claims 1, 2, 4, 5, 8, 19-22, 24, and 25 of the '540 patent against Ariosa. A0004 (4:13–15).

On January 6, 2012 and February 22, 2012, respectively, Natera and Verinata initiated declaratory judgment actions against Sequenom seeking judgments that their products do not infringe the ’540 patent and that all claims of the ’540 patent are invalid. A0093 (Dkt. No. 1); A0115 (Dkt. No. 1). Sequenom counterclaimed against each of them for infringement.[2] A0096 (Dkt. No. 40); A0116 (Dkt. No. 15). The three cases among Sequenom, Natera, Verinata, and Ariosa were related and coordinated for purposes of claim construction and scheduling. A0062 (Dkt. No. 41).

On July 5, 2012, the District Court issued an Order denying Sequenom’s preliminary injunction motion against Ariosa. A0071 (Dkt. No. 121). Sequenom appealed. *Id.* (Dkt. No. 123). On August 9, 2013, this Court vacated and remanded. *Aria Diagnostics, Inc.*, 726 F.3d at 1305. In vacating the District Court’s Order, this Court offered no opinion “as to whether there is or is not a substantial question regarding the subject matter eligibility of the asserted claims” of the ’540 patent. *Id.* at 1304. This Court remanded “for the district court to examine subject matter eligibility … in light of *Myriad* and the different claim construction” in this Court’s decision. *Id.*

[2] Sequenom asserted two additional claims against Natera and DDC (claims 13 and 18), A0024 (1:16-17), and six additional claims against Verinata (claims 6, 7, 12, 13, 15, and 18). A0030 (1:18-19).

After remand, on August 16, 2013, Ariosa filed a motion for summary judgment that each asserted claim of the ’540 patent is invalid as not drawn to patent-eligible subject matter. A0080 (Dkt No. 219). Sequenom opposed and filed a “Cross-Motion for Partial Summary Judgment on Section 101 Patent Eligibility.” A0081 (Dkt. No. 223).

On October 30, 2013, after full briefing and a hearing at which both Ariosa and Sequenom made arguments to the Court, A3500-43, the District Court granted Ariosa’s summary judgment motion, thus invalidating the claims, and denied Sequenom’s cross-motion. A0084 (Dkt. No. 254). The Court concluded that, “based on the undisputed facts before the Court, Ariosa has met its burden of proving by clear and convincing evidence that [the asserted claims] of the ’540 patent are not drawn to patent-eligible subject matter and are invalid under 35 U.S.C. § 101.” A0020 (20:3-5) (2013 WL 5863022 (N.D. Cal. Oct. 30, 2013)). The District Court noted Sequenom’s *agreement* “that neither cffDNA nor the discovery of cffDNA in maternal plasma or serum is patentable, because the presence of cffDNA in maternal plasma or serum is a natural phenomenon.” A0012 (12:14-15). The District Court further found that the claims are directed to “methods of detecting paternally inherited cffDNA in maternal plasma or serum,” *id*. (12:21-22), that “merely apply ‘conventional techniques’ [of fractionation, amplification and detection] to the newly discovered natural phenomenon....” A0014 (14:13-14). The District Court

concluded that these claimed steps were "well-understood, routine, and conventional activity at the time of the invention" and that the "evidence shows that it was well-understood, routine, and conventional activity to combine these steps to detect DNA in serum or plasma." A0018 (18:6-9).

As a result, the District Court found that the asserted claims of the '540 patent fail to recite patent-eligible subject matter because "looking at the claimed processes as a whole, the only inventive component of the processes in the '540 patent is to apply those well-understood, routine processes to paternally inherited cffDNA, a natural phenomenon." *Id.* (18:11-13). The District Court also considered "whether the [asserted claims of the '540 patent] pose[] a risk of preempting a law of nature, natural phenomenon, or abstract idea." A0018 (18:14-15). Despite three articles that, according to Sequenom, disclose non-infringing ways of using cffDNA, the District Court found that the scope of the asserted claims did pose a substantial risk of doing so. A0019-20 (19:27-20:2).

On December 2, 2013, Sequenom filed a Notice of Appeal in each of the related cases.[3] A0085 (Dkt. No. 265); A0130 (Dkt. No. 153); A0105-06 (Dkt. No. 146). This Court consolidated the appeals on December 23, 2013. Sequenom filed its consolidated opening brief on January 22, 2014. Two *amici curiae*, Biotechnology

[3] Sequenom, Natera, and Verinata stipulated to final judgments on all issues related to the '540 patent for purposes of this appeal. A0023-33.

Industry Organization ("BIO") and San Diego Intellectual Property Law Association, Inc. ("SDIPLA"), filed briefs in support of Sequenom's position on January 28, 2014. Appellees provide this consolidated brief in response.

SUMMARY OF ARGUMENTS

The '540 patent begins with the proclamation that it "has now been discovered that foetal DNA is detectable in maternal serum or plasma samples." A0039 (1:50-51). There is no dispute that the applicants' claimed discovery—the presence of cffDNA in maternal serum and plasma—is a natural phenomenon. *See* Br. at 19. Nor is there any dispute that the discovery of a natural phenomenon is not patentable subject matter. *E.g.*, *id.* at 32. The '540 patent is invalid because its claims are broadly directed to the detection of a natural phenomenon, without any meaningful limitations that prevent the patent from disproportionately tying up too much use of this natural phenomenon.

On appeal, Sequenom has defended the validity of the '540 patent based on three "steps" that purportedly can be found in the independent claims of the patent.[4]

[4] Sequenom does not address in its opening brief whether any dependent claims survive the patent-eligibility analysis based on their additional limitations. Thus, Sequenom has waived any argument that the District Court erred in finding that the additional limitations in the dependent claims make no difference to the outcome of the patent-eligibility analysis. *E*.g., *Engel Industries, Inc. v. Lockformer Co.*, 166 F.3d 1379, 1383 (Fed. Cir. 1999) ("An issue that falls within the scope of the judgment appealed from but is not raised by the appellant in its opening brief on appeal is necessarily waived."). It is particularly improper for Sequenom to argue for the patentability of any dependent claims for the first time on reply. *See, e.g.*, *Aventis*

Claim 1 is representative—and demonstrates precisely why the District Court was correct to conclude that the ’540 patent fails to recite patent-eligible subject matter. Claim 1 is set forth below, and its broad, circular language has been highlighted:

> A method for ***detecting a paternally inherited nucleic acid of fetal origin performed on a maternal serum or plasma sample*** from a pregnant female, which method comprises
>
> amplifying a paternally inherited nucleic acid from the serum or plasma sample and
>
> ***detecting the presence of a paternally inherited nucleic acid of fetal origin in the sample.***

In an effort to differentiate claim 1 from the natural phenomenon of cffDNA in maternal serum or plasma, Sequenom characterizes claim 1 as involving three steps: (1) fractionating maternal blood to produce plasma or serum samples; (2) amplifying a paternally inherited nucleic acid from the serum or plasma sample; and (3) detecting the presence of a paternally inherited nucleic acid of fetal origin in the sample. *E.g.*, Br. at 4. In reality, Sequenom’s three-step construct is little more than a legal fiction.

Aside from the amplification step, the language of claim 1 is circular and devoid of content: “A method for ***detecting a paternally inherited nucleic acid of fetal origin performed on a maternal serum or plasma sample*** from a pregnant

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Pharma S.A. v. Hospira, Inc., 675 F.3d 1324, 1332 (Fed. Cir. 2012) (argument that patent claim was not invalid waived when raised for first time on reply).

female, which method comprises ... ***detecting the presence of a paternally inherited nucleic acid of fetal origin in the sample***." A0050. The claim recites nothing that limits or describes the manner by which the fetal nucleic acid is detected. The amplification step, which this Court has broadly construed to mean merely making more copies of the fetal nucleic acid, includes nothing that limits or describes the manner by which copies of fetal nucleic acid are made, the number of copies that would satisfy the claim, or how the copies are detected.[5]

In its most recent decision on the non-patentability of a natural phenomenon—*Association for Molecular Pathology v. Myriad Genetics, Inc.*, 133 S. Ct. 2107 (2013)—the Supreme Court found that claims directed to the naturally occurring DNA sequence of genes responsible for increased risk of breast and ovarian cancer are not patent eligible. *Id.* at 2111. Just as the discovery of these genes falls outside the scope of patentability, so too does the claimed discovery of cffDNA in maternal plasma and serum. The genes in *Myriad* and the cffDNA in this case are simply phenomena of nature. Their discovery cannot be patented under this binding precedent.

[5] It is noteworthy that the amplification step was added at the insistence of the PTO to address enablement concerns—having enough copies of cffDNA in the sample to detect—and not by the inventors as a meaningful limitation on the scope of the claim or to distinguish anything in the prior art. A1036-37 (17:18-18:4). But for the last-minute intervention of the PTO, claim 1 truly would have been devoid of any limitation whatsoever on the use of the natural phenomenon at issue.

Moreover, before its decision in *Myriad*, the Supreme Court reaffirmed its longstanding rule that the prohibition on patenting a natural phenomenon cannot be overcome through the artifice of grafting "well-understood, routine, conventional activity" onto that phenomenon. In *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, 132 S. Ct. 1289 (2012), the Supreme Court cautioned that its prior decisions "insist that a process that focuses upon the use of a natural law ***also contain other elements or a combination of elements, sometimes referred to as an 'inventive concept***,' sufficient to ensure that the patent in practice amounts to significantly more than a patent upon the natural law itself." *Id.* at 1294 (emphasis added). Relying upon this longstanding principle, the Supreme Court concluded that a natural phenomenon does not become patentable merely by claiming "additional steps [that] consist of well-understood, routine, conventional activity already engaged in by the scientific community; and those steps, when viewed as a whole, add nothing significant beyond the sum of their parts taken separately." *Id*. at 1298. Said another way, "well-understood, routine, conventional activity" does not meet the "inventive concept" requirement mandated by Supreme Court precedent.

The '540 patent does not pass muster under *Mayo*, *Myriad*, or the decades of Supreme Court precedents before them. Indeed, claim 1 has far less substance than the claims examined in *Mayo* and *Myriad*. Claim 1 does not say anything about the method of detecting paternally inherited cffDNA, other than it must include making

more copies of the cffDNA to be detected—and claim 1 does not even say anything about the method of making more copies of cffDNA. As a result, claim 1 does not recite any "inventive concept"—*i.e.*, "other elements or a combination of elements … sufficient to ensure that the patent in practice amounts to significantly more than a patent upon the natural law itself." Quite to the contrary; the patent instructs those skilled in the art to use *any* well-known technique to detect fetal nucleic acids. That is *exactly* how the applicants described their invention to the PTO during prosecution:

> [I]t is not necessary for the Applicants to set out each of the many ways in which DNA might be analyzed. The description is sufficient simply by instructing one skilled in the art to carry out a suitable analysis.... ***[O]ne skilled in the art is readily able to apply the teachings of the present application to any one of the well known techniques for detection of DNA with a view to analysis of foetal DNA in [m]aternal plasma or serum.***

A1054-55 (emphasis added).

Sequenom makes four primary arguments on appeal. Each is without merit.

First, Sequenom argues that the '540 patent claims recite patent-eligible subject matter because, prior to the inventors' discovery, no one had looked in maternal serum or plasma to find naturally occurring cffDNA. To Sequenom, that "stroke of genius," Br. at 2, combined with the instruction to amplify and detect cffDNA, constitutes a patentable method. Sequenom is wrong. The claimed method boils down to instructions to (i) look in a certain place for cffDNA (the cell-free

portion of whole blood, which is the same place other types of cell-free DNA had been previously detected), (ii) make many copies of that cffDNA (by any known means), and (iii) detect the presence of that cffDNA (by any known means). In essence, Sequenom does no more than tout, as *the* patentable subject matter, that the applicants allegedly were the first to detect this natural phenomenon. No meaningful limitations—or what the Supreme Court has called an "inventive concept"—can be found in the broad and circular claim language directed to simply detecting this natural phenomenon.

Nor can the *particular type of DNA* to be detected distinguish the claim as patentable subject matter, even if the applicants were the first to discover its presence in maternal plasma and serum. As Sequenom concedes, the discovery of a previously unknown natural phenomenon is not patentable. And the '540 patent purports to cover any and every method of detecting the presence of this natural phenomenon—cffDNA in serum and plasma—so long as extra copies of the cffDNA (no matter how few and no matter how made) are produced as part of the method. These are not meaningful limitations on a claim covering the discovery of a natural phenomenon, particularly given that the patent *solely* teaches (as Sequenom concedes) amplification and detection techniques for DNA that were well-known, routine and conventional as of the patent's priority date. A3520 (21:19-21) (concession by Sequenom that "if you go through all the elements in the claim you

could put a check as either a conventional item or a natural phenomenon" next to each element). Indeed, as the '540 patent itself recites, these very same techniques had previously been used to detect other types of cell-free DNA (specifically, tumor DNA) in plasma and serum. A0039 (1:40-44).

Second, Sequenom argues that the Supreme Court's decision in *Myriad* supports its challenge to the District Court's decision. It does not. The applicants' discovery of cffDNA is no more patentable than Myriad's discovery of the naturally occurring sequence of the BRCA1 and BRCA2 genes. Although no method claims were challenged, the Supreme Court noted that Myriad *might* have successfully claimed patentable subject matter *if* it had "created an innovative *method*" of isolating those genes. 133 S. Ct. at 2119 (emphasis added). Like Myriad, however, the applicants here did not create an innovative method of detecting naturally occurring DNA that might pass the patent eligibility threshold.

In an argument never made to the District Court (and therefore waived),[6] Sequenom strains on appeal to analogize the broad and circular amplification-and-detection language from the '540 patent to the laboratory-manufactured cDNA that the Supreme Court found patentable in *Myriad*. There is no analogy to be made: The claimed method of the '540 patent does not

[6] "The general rule is that this court does not consider arguments not raised below." *Celsis in Vitro, Inc. v. Cellzdirect, Inc.*, 664 F.3d 922, 931 (Fed. Cir. 2012).

create anything except more copies of naturally occurring cffDNA. Nothing in the claim language requires the creation of anything new, in contrast to the cDNA sequence ***expressly recited*** in the claim found to be patent-eligible in *Myriad*. Moreover, *Myriad* is clear that any structural differences that may appear in amplified cffDNA would be an insufficient basis for patent eligibility, particularly where (as here) such differences are not even described in the '540 patent claim language. *Id.* at 2118. Sequenom again argues that the asserted claims are just as patentable as a claim 21 in a Myriad patent, but no case from any court (including the Supreme Court) has ever addressed the patentability of that claim 21.

Third, Sequenom contends that a method that does not wholly preempt all uses of a natural phenomenon is, "*by definition,*" patent eligible. Br. at 30 (emphasis added). That is not the law. In *Mayo*, the Supreme Court reaffirmed that, while preemption is an important consideration, it is not ***the*** determinative factor. *See* 132 S. Ct. at 1301-02. Both Chief Judge Rader and Judge Lourie acknowledged that principle in their separate opinions in *CLS Bank International v. Alice Corporation Pty. Ltd. E.g.*, 717 F.3d 1269, 1300 (Fed. Cir. 2013) (Rader, J.) (stating that even "if a claim does not wholly pre-empt an abstract idea" it will not be patent eligible "if it contains only insignificant or token pre- or post-solution activity"); *id.* at 1281 (stating that "the proper focus is not preemption *per se*," as "a patent-eligible claim must include one or more substantive limitations …"). Although complete

preemption may signal invalidity, the converse is not true: the absence of complete preemption does not demonstrate patent eligibility.

Finally, Sequenom contends that, because three "peer reviewed" articles allegedly disclose non-infringing means of detecting cffDNA, there is no complete preemption and therefore the asserted claims are patent eligible. This argument is derivative of Sequenom's legally flawed third argument—that patent eligibility is solely a function of demonstrating the absence of complete preemption of the relevant natural phenomenon. That is not the test for patent eligibility.

Moreover, because all three articles post-date the issuance of the '540 patent, they are legally irrelevant to the patent-eligibility determination, which (like all other validity determinations) is assessed as of the priority date of the patent. Whether the claims of the '540 patent recite an "inventive concept" apart from the natural phenomenon of cffDNA, and whether the claims disproportionately tie up too much use of that natural phenomenon, are inquiries to be determined as of the applicable priority date—not based upon later developments in the field.

The alternative approach promoted by Sequenom finds no support in any decision of the Supreme Court or this Court. Such an approach would improperly turn a question of law into a question of fact whose outcome would depend on an ever-changing factual landscape: The patentability of a claimed invention could change from one year to the next depending on what alternative uses were found (or

not found) in the interim. That is not the law. In any event, as the District Court correctly concluded, none of Sequenom's articles identifies a "substantial practical application" of the discovery of cffDNA. *Mayo*, 132 S. Ct. at 1301 (claimed method must not preempt all "substantial practical application[s]" of the natural phenomenon). As such, even if they were relevant, those articles do not change the outcome of this appeal.

None of Sequenom's arguments succeeds in demonstrating that the claims of the '540 patent are addressed to patent-eligible subject matter. Accordingly, as discussed in detail below, this Court should affirm the District Court's grant of summary judgment.

ARGUMENT

I. The Discovery of a Natural Phenomenon, Such as Cell-Free Fetal DNA in Maternal Serum or Plasma, Is Not Patent-Eligible Subject Matter

Section 101 of the Patent Act provides: "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor...." 35 U.S.C. § 101. The Supreme Court "has long held" that Section 101 contains an important exception: "'[L]aws of nature, natural phenomena, and abstract ideas' are not patentable." *Mayo*, 132 S. Ct. at 1293 (quoting *Diamond v. Diehr*, 450 U.S. 175, 185 (1981)). It is well established, therefore, that "[h]e who discovers a hitherto

unknown phenomenon of nature has no claim to a monopoly of it which the law recognizes." *Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127, 130 (1948). "Such discoveries are manifestations of nature, free to all men and reserved exclusively to none." *Mayo*, 132 S. Ct. at 1293 (internal quotation marks omitted).

The Supreme Court has applied this principle consistently for many years to invalidate patents that claim the discovery of a natural phenomenon. In *Funk Brothers*, the Supreme Court invalidated a patent covering the discovery that certain naturally occurring bacteria strains could be mixed together to promote the growth of various leguminous plants because the patent reflected "no more than the discovery of some of the handiwork of nature...." 333 U.S. at 131. The Supreme Court acknowledged that, "though [the discovery] may have been the product of skill, it certainly was not the product of invention. There is no way in which we could call it such unless we borrowed invention from the discovery of the natural principle itself." *Id*. at 132.

The Supreme Court most recently applied this prohibition against patenting a natural phenomenon in *Myriad.* There, the Court found that Myriad's claims covering isolation of the BRCA1 and BRCA2 genes are not drawn to patent-eligible subject matter. The Court observed that:

> Myriad did not create or alter any of the genetic information encoded in the BRCA1 and BRCA2 genes. The location and order of the nucleotides existed in nature before Myriad found them. Nor did Myriad create or alter

> the genetic structure of DNA. Instead, Myriad's principal contribution was uncovering the precise location and genetic sequence of the BRCA1 and BRCA2 genes within chromosomes 17 and 13.

133 S. Ct. at 2116. Rejecting patent protection for this discovery, the Court reasoned that Myriad "found an important and useful gene, but separating that gene from its surrounding genetic material is not an act of invention." *Id*. at 2117. The Court emphasized that "the processes used by Myriad to isolate DNA were well understood by geneticists at the time of Myriad's patents ... and are not at issue in this case." *Id*. at 2119-20. In contrast, the Court upheld Myriad's claims directed to cDNA—laboratory synthesized, non-naturally occurring versions of the BRCA1 and BRCA2 genes that exclude those portions of the genes (called introns) that do not code for the expression of amino acids. *Id*. at 2119. The Court found that, unlike the act of isolating a naturally occurring gene, a "lab technician unquestionably creates something new when cDNA is made." *Id*.

Here, the '540 patent recites that the inventors "discovered that foetal DNA is detectable in maternal serum or plasma samples." A0039 (1:50-51). There can be no dispute that paternally inherited cffDNA in maternal serum or plasma is a natural phenomenon which, like the BRCA1 and BRCA2 genes, "existed in nature before [they were] found." *Myriad*, 133 S. Ct. at 2116. It makes no difference that the patent describes this discovery as "a surprising and unexpected finding." A0039 (1:51-55). Surprising or not, "[g]roundbreaking, innovative, or even brilliant discovery does

not by itself satisfy the § 101 inquiry." *Myriad*, 133 S. Ct. at 2117. As such, the applicants' claimed discovery "may have been the product of skill, [but] certainly was not the product of invention." *Funk Bros.*, 333 U.S. at 132.

II. Supreme Court Authority Requires Method Claims That Focus on the Use of a Natural Phenomenon to Recite an "Inventive Concept" Apart from the Natural Phenomenon In Order to Cover Patent-Eligible Subject Matter

The Supreme Court's core inquiry for patent eligibility is as follows: "[D]o the patent claims add *enough* to their statements of the [natural law or phenomenon] to allow the processes they describe to qualify as patent-eligible processes that *apply* natural laws?" *Mayo*, 132 S. Ct. at 1297 (emphasis in original). The answer depends on whether the asserted claims recite an "inventive concept" *in addition to* the natural law or phenomenon. Without that inventive concept, a patent claim that focuses on the use of a natural phenomenon does not cover patent-eligible subject matter.

The Supreme Court in *Mayo* recognized that its longstanding precedent "insist[s] that a process that focuses upon the use of a natural law ***also contain other elements or a combination of elements, sometimes referred to as an 'inventive concept***,' sufficient to ensure that the patent in practice amounts to significantly more than a patent upon the natural law itself." *Id.* at 1294 (emphasis added). The Supreme Court has repeatedly instructed that the inquiry into whether an inventive concept is present requires considering the claims "as if the principle or

mathematical formula were well known," *Parker v. Flook*, 437 U.S. 584, 592 (1978), and "putting the [natural phenomenon] to the side" to determine whether the claims include the requisite inventive concept. *Mayo*, 132 S. Ct. at 1299 (other steps "were all 'well known,' to the point where, putting the formula to the side, there was no 'inventive concept' in the claimed application of the formula") (quoting *Flook*, 437 U.S. at 594).[7]

The Supreme Court has been vigilant in rejecting the patentability of claims that simply combine a law of nature, natural phenomenon, or abstract idea with other claim limitations that fail to recite an inventive concept. For example, in *Flook*, the Supreme Court explained that the discovery of "a phenomenon of nature or mathematical formula ... cannot support a patent *unless there is some other inventive concept in its application*." 437 U.S. at 594 (emphasis added). The Supreme Court invalidated a claimed method whose only inventive aspect was a mathematical formula for updating alarm limits and where all other elements reflected "conventional methods of changing alarm limits." *Id.* at 585-86. The Supreme Court reasoned that a "competent draftsman could attach some form of post-solution

[7] Amicus SDIPLA urges this Court to adopt a rule that any "claim to a new use of a known process or composition of matter that applies a law of nature or natural phenomenon without claiming it" is patent eligible even in the absence of an inventive concept. *E.g.*, SDIPLA Br. at 10. This proposed rule runs contrary to decades of Supreme Court precedent. *E.g.*, *Mayo*, 132 S. Ct. at 1297. In any event, the claims here make no application of the discovery whatsoever.

activity to almost any mathematical formula; the Pythagorean theorem would not have been patentable, or partially patentable, because a patent application contained a final step indicating that the formula, when solved, could be usefully applied to existing surveying techniques." *Id.* at 590.

III. In *Mayo*, the Supreme Court Held that the "Inventive Concept" Requirement Is Not Satisfied by Combining a Natural Phenomenon with Well-Understood, Routine or Conventional Activity

In *Mayo*, the Supreme Court further elucidated the "inventive concept" requirement in the context of method claims centered around the use of a natural phenomenon in the life sciences. The Court held that the prohibition on patenting a natural phenomenon cannot be overcome by combining that phenomenon with additional steps that "consist of well-understood, routine, conventional activity already engaged in by the scientific community; and those steps, when viewed as a whole, add nothing significant beyond the sum of their parts taken separately." *Mayo*, 132 S. Ct. at 1298. The Court ruled "that simply appending conventional steps, specified at a high level of generality, to laws of nature, natural phenomena, and abstract ideas cannot make those laws, phenomena, and ideas patentable." *Id*. at 1300.

The Supreme Court's application of these principles in *Mayo* is instructive here. At issue in *Mayo* were "processes that help doctors who use thiopurine drugs to treat patients with autoimmune diseases determine whether a given dosage level is

too low or too high." *Id.* at 1294. The claims purported "to apply natural laws describing the relationships between the concentration in the blood of certain thiopurine metabolites and the likelihood that the drug dosage will be ineffective or induce harmful side-effects." *Id*. The Court began its analysis by observing that "Prometheus' patents set forth laws of nature—namely, relationships between concentrations of certain metabolites in the blood and the likelihood that a dosage of a thiopurine drug will prove ineffective or cause harm." *Id.* at 1296. The Court then considered whether "the patent claims add *enough* ... to allow the processes they describe to qualify as patent-eligible processes that apply natural laws[.]" *Id*. at 1297 (emphasis in original).

Dividing the method claim into its three steps—an "administering" step, a "wherein" step, and a "determining" step—the Court looked at the steps separately and in combination to conclude that they did not add anything "sufficient to transform the nature of the claim:"

- "First, the 'administering' step simply refers to the relevant audience .... That audience is a pre-existing audience; doctors used thiopurine drugs to treat patients suffering from autoimmune disorders long before anyone asserted these claims." *Id.*
- "Second, the 'wherein' clauses simply tell a doctor about the relevant natural laws ...." *Id.*

- "Third, the 'determining' step tells the doctor to determine the level of the relevant metabolites in the blood, through whatever process the doctor or laboratory wishes to use." *Id.* The Court found that determining the level of metabolites in the bloodstream "through whatever process the doctor or the laboratory wishes to use" requires no more than "well-understood, routine, conventional activity previously engaged in by scientists who work in the field." *Id.* at 1297-98.

Whether analyzed separately or in combination, *id*. at 1298, these additional steps failed to "add *enough* … to allow the processes they describe to qualify as patent-eligible processes that *apply* natural laws." *Id*. at 1297; *see also id*. ("These additional steps are not themselves natural laws but neither are they sufficient to transform the nature of the claim."). Rather, the claimed steps added "nothing specific to the laws of nature other than what is well-understood, routine, conventional activity, previously engaged in by those in the field." *Id*. at 1299.

Here, the District Court correctly concluded that the claimed methods of the '540 patent "apart from the natural phenomenon of paternally inherited cffDNA—involve no more than well-understood, routine, conventional activity,

previously engaged in the field" and thus they "are not drawn to patent-eligible subject matter and are invalid under § 101." A0015 (15:4-6).[8]

IV. The '540 Patent Claims Are Invalid Because They Rely upon Well Understood, Routine, and Conventional Activity and Thus Fail to Recite an "Inventive Concept" in Addition to the Natural Phenomenon of cffDNA

Sequenom characterizes the method claimed in the '540 patent as involving three steps: (1) fractionating maternal blood to produce plasma or serum samples; (2) amplifying a paternally inherited nucleic acid from the serum or plasma sample; and (3) detecting the presence of a paternally inherited nucleic acid of fetal origin in the sample. *E.g.*, Br. at 4. This characterization truly exalts form over substance: Aside from the amplification step, the language of claim 1 is entirely circular: "A method for detecting a paternally inherited nucleic acid of fetal origin performed on a maternal serum or plasma sample from a pregnant female, which method

[8] On March 4, 2014, the PTO issued a memorandum providing guidance to patent examiners on subject matter eligibility analysis of claims involving the judicial exceptions of natural laws, phenomena, and products. A3544-3562 ("PTO Memorandum"). While such guidance is "not binding on this [C]ourt, … [it] may be given judicial notice to the extent [it] does not conflict with the statute." *Enzo Biochem, Inc. v. Gen-Probe Inc*., 323 F.3d 956, 964 (Fed. Cir. 2002). The summary of precedent and list of relevant factors contained in the PTO Memorandum reflect the current law and the analytical framework that Appellees have used in this case. Among those factors, the PTO pointed out the need for "meaningful limits on claim scope … so that others are not substantially foreclosed from using the judicial exception(s)" and that "do more than describe the judicial exception(s) with general instructions to apply or use" them. A3548-49. The PTO also pointed out the need for "one or more elements/steps in addition to the judicial exception(s) that add a feature that is more than well-understood, purely conventional or routine in the relevant field." *Id*. at A3548. The '540 patent claims fail both of these eligibility tests.

comprises ... detecting the presence of a paternally inherited nucleic acid of fetal origin in the sample." A0050. There are no limitations on how plasma or serum is fractionated from whole blood, or how cffDNA is detected or amplified in plasma or serum. According to Sequenom, any method that detects the presence of paternally inherited cffDNA in plasma or serum would fall within the scope of the '540 patent, so long as extra copies of that cffDNA (no matter how few) are made when performing the method.

Even assuming that the asserted claims can be fairly characterized as reciting a three-step method, those steps are not sufficient to transform the claims into a patentable application of the discovery of cffDNA. As in *Mayo*, they consist, at most, of "conventional activity previously engaged in by scientists who work in the field." *Mayo,* 132 S.Ct. at 1297-98. In fact, the pedestrian limitations of "look in" maternal serum and plasma, "make more" DNA, and "find" the DNA—all through means explained in the specification and during prosecution as well known and routine—make clear that the District Court was correct to conclude that "the only inventive part of the patent is that conventional techniques of DNA detection known at the time of the invention are applied to paternally inherited cffDNA as opposed to other types of DNA. Thus, the only inventive concept contained in the patent is the discovery of cffDNA, which is not patentable." A0015 (15:18-21).

A. The "Fractionating" Step Was Well-Understood, Routine, and Conventional in 1997

Sequenom does not contend that any claim recites anything unconventional about the fractionating step, which simply involves employing a centrifuge to isolate plasma and serum through the removal of cells from whole blood collected from a pregnant woman. Br. at 5. This claim step adds nothing of significance to the putative invention. Indeed, as the '540 patent itself explains, "[t]he preparation of serum or plasma from the maternal blood is carried out *through standard techniques*." A0039 (2:26-27) (emphasis added). No specific method of fractionation—let alone a new method—is required by the '540 patent.

Sequenom focuses on the fact that plasma and serum, *i.e.*, the result of the fractionating, "are what was previously discarded as waste by researchers looking for fetal DNA in intact fetal cells." Br. at 5-6. Sequenom contends it was an inventive concept to *look in* this previously-discarded serum and plasma, which resulted from existing methods of fractionating, to find the naturally occurring cffDNA. A3518 (19:6-10) ("The inventive concept was to take a known method and to look ... in a place where people were ... throwing it away.").

But in the same way it is not sufficient to "simply state the law of nature while adding the words 'apply it,' *Mayo*, 132 S. Ct. at 1294, it is not sufficient to simply identify naturally occurring cffDNA and instruct one to "look for it" in serum or plasma (which themselves are naturally occurring parts of whole blood) that are

separated through known methods of fractionating. In reality, that amounts to little, if anything, more than a recitation of the natural phenomenon itself—the presence of cffDNA in maternal serum or plasma.

B. The "Amplifying" Step Was Well-Understood, Routine, and Conventional in 1997

With respect to the "amplifying" step, the District Court construed "amplifying" as "increasing the amount ... by making copies of it," as required by this Court. A1253 (7:4-5). At its rudimentary level, the "amplifying" step simply directs one to increase the amount (by making copies) of the naturally occurring cffDNA through whatever means one wishes. This instruction to "make more of it" fails to add anything of significance to the naturally occurring cffDNA.[9] In the same way it is not sufficient to "simply state the law of nature while adding the words 'apply it,'" *Mayo*, 132 S. Ct. at 1294, it is not sufficient to simply identify naturally occurring cffDNA and instruct one to "make more of it."

Moreover, it is undisputed that amplification was well known by 1997. For example, the '540 patent itself acknowledges that, "[a]n amplification of foetal DNA sequences in the sample is normally carried out. *Standard nucleic acid amplification*

[9] Sequenom may seek to analogize to one example claim in the PTO Memorandum, but the analogy fails. Claim 2 of Example E recites a "method of amplifying a target DNA" with multiple limitations. A3555-57. In contrast, although the '540 patent includes "amplifying," it contains no limitations akin to those in Example E. Instead, the '540 patent encompasses *any known method of amplification, applied in any way*, and the term has been broadly construed to mean "increasing the amount … by making copies of it." A1253.

systems can be used....” A0039 (2:43-45) (emphasis added). Sequenom previously admitted that “[a] variety of ***common methods*** of amplifying nucleic acids are referenced in the patent, including perhaps the most-widely used, polymerase chain reaction (‘PCR’).” A1124 (8:25-27) (emphasis added). Moreover, Dr. Lo declared during prosecution that “[s]uitable amplification techniques can be ordinary PCR or more sophisticated developments thereof, *but these techniques were all known in the literature before the date of my invention.*” A1109 (¶ 7) (emphasis added).

Dr. Mark Evans, an expert retained by Sequenom, also admitted that “***[v]arious methods of amplification were known*** back in 1997, but the most common is called the ‘polymerase chain reaction,’ or ‘PCR,’ which was invented in the 1980’s.” A1160 (¶ 42) (emphasis added). And, when asked during his deposition “[h]ow would a person of skill in the art know in 1997 how you would, for example, amplify paternally inherited nucleic acids from the serum or plasma?”—the precise language of the claim—Dr. Evans replied that “[t]he technique of the polymerase chain reaction was already well known in science at that time as well as other methodologies which could be used.” A1092-93 (150:18-151:5).

C. The “Detecting” Step Was Well-Understood, Routine, and Conventional in 1997

Like the “amplifying” step, the “detecting” step is specified at a high level of generality—no specific technique is required—and simply instructs one to detect paternally inherited cffDNA in maternal plasma or serum through whatever process

one desires. The District Court's construction of "detecting" was "discovering or determining the existence, presence, or fact of." A1255 (9:6-7). The "detecting" step thus simply directs one to discover or determine the existence, presence, or fact of naturally occurring paternally inherited nucleic acid of fetal origin in the serum or plasma sample—by any method whatsoever. Significantly, the claim does not teach *how* to detect cffDNA in serum or plasma; it simply says "detect it." As with the other steps of the claim, it is no more sufficient to recite a natural phenomenon along with the words "find it" than it is to recite a law of nature along with the words "apply it." *See Mayo*, 132 S. Ct. at 1294.

Sequenom does not dispute that DNA detection in serum and plasma was well known by 1997. The '540 patent specification gives examples of methods already used to detect other nucleic acids in serum or plasma: For example, by 1996, others had "demonstrated that tumour DNA can be detected by the polymerase chain reaction (PCR) in the plasma or serum ...." A0039 (1:40-42). Moreover, the applicants made numerous statements during prosecution that confirm the "detecting" step was well-understood, routine, and conventional as of 1997:

- "[O]ne skilled in the art is aware of a ***variety of techniques which might be used to detect different nucleic acid species***.... ***These techniques are a matter of routine*** for one skilled in the art for the analysis of DNA." A1052 (emphasis added).

- "[O]ne skilled in the art is readily able to apply the teachings of the present application to any one of the ***well known techniques for detection*** of DNA with a view to analysis of foetal DNA in [m]aternal plasma or serum." A1054-55 (emphasis added).
- "The person skilled in the art has a broad range of techniques available for the detection of DNA in the sample." A1057.

Dr. Lo also confirmed during prosecution that there "is sufficient fetal DNA present in the maternal serum for ***detection by conventional PCR***. These detectable quantities of DNA could be utilised by those skilled in the art ***to detect any target sequence*** within the DNA, just by the use of the appropriate primer sequence in relation to that target." A1104-05 (¶ 4(d)) (emphasis added).

Similarly, when Sequenom's expert Dr. Evans was asked during his deposition how a person of skill in the art would know of "the techniques for how to look for that [fetal] DNA" in maternal plasma, he replied that "[t]echniques such as the polymerase chain reaction were known in the field at that point," which could be used to detect fetal DNA. A1095-96 (155:23-156:11).[10]

[10] The District Court's invalidity determination extended to the dependent claims of the '540 patent asserted against Ariosa. A0014 (n.5); A0020 (20:3-5). Sequenom, Verinata, Natera, and DDC stipulated that it would also extend to six other dependent claims if not reversed. Br. at 4-5 n.1. As discussed *supra* at n. 4, Sequenom has waived any argument on appeal with respect to any dependent claims.

D. The Claimed Steps Were Routinely Used In Combination to Detect Nucleic Acid before 1997

Sequenom complains that the District Court improperly "dissected" the steps of the '540 patent's claimed method, without considering the steps in combination, to determine whether that method contained any inventive concept. That complaint is meritless: The District Court explained that it had "considered the claimed processes as a whole." A0018 (18:5-6). Having done so, the District Court concluded that "[t]he unrebutted evidence does not merely show that the individual steps of fractionation, amplification, and detection were well-understood, routine, and conventional activity at the time of the invention. The evidence shows that [it] was well-understood, routine, and conventional activity to ***combine*** these steps to detect DNA in serum or plasma." *Id*. (18:6-9) (emphasis added).

Moreover, the District Court followed the Supreme Court's methodology in *Mayo*, in which the Supreme Court considered a three-step process that recited an "administering" step, a "wherein" step, and a "determining" step. *Mayo*, 132 S. Ct. at 1297-98. To analyze whether the steps were "sufficient to transform the nature of the claim," the Supreme Court examined each step individually, but also concluded that "to consider the three steps *as an ordered combination* adds nothing to the laws of nature that is not already present when the steps are considered separately." *Id*. at 1297-98 (emphasis added). In sum, the Court noted, any additional steps beyond the laws of nature at issue consisted of "well-understood, routine, conventional activity

already engaged in by the scientific community; *and those steps, when viewed as a whole, add nothing significant beyond the sum of their parts taken separately*." *Id*. (emphasis added). Here, the District Court followed this methodology exactly, first examining the inventive concept of each step separately, and then doing so in combination. A0013-18 (13:14-18:13).

Sequenom's complaint that the evidence the District Court cited was "neither clear nor convincing" is similarly meritless. The District Court correctly recognized that it was well known before the '540 patent to use the *combination* of fractionation, amplification and detection as a method of detecting nucleic acid in serum or plasma. A0018 (18:8-9). For example, Sequenom's expert testified to *this very fact* at his deposition. A1237 (188:5-13). Dr. Evans also testified that others before Dr. Lo amplified and detected nucleic acid specifically *in plasma and serum*. *Id*. (188:15-17).

Finally, the combination of claimed steps was routinely practiced by molecular biologists for detecting nucleic acid in related fields by 1997. The '540 patent specification itself states that "it has been demonstrated that tumour DNA can be detected by the polymerase chain reaction (PCR) in the plasma or serum of some patients (Chen et al 1996; Nawroz et al 1996)." A0039 (1:40-43). And Drs. Lo and Wainscoat have stated it was prior research involving detection of tumor DNA in plasma or serum that prompted them to use the same steps in combination to look for

cell-free fetal DNA. A1241 ("[T]there have been reports that tumour DNA can be detected by molecular techniques in the plasma or serum of cancer patients. Such reports prompted us to investigate whether fetal DNA can be detected in maternal plasma and serum."). Thus, the isolation of plasma or serum from whole blood combined with the amplification and detection of nucleic acid by PCR was conventional and well-known by those skilled in the art, including the applicants themselves.

Sequenom protests that the unconventional activity here—*i.e.*, the inventive concept—is that "before the '540 patent, no one was using the plasma or serum of pregnant mothers to amplify and detect paternally-inherited cffDNA." Br. at 49; *see also* BIO Br. at 22-23. Sequenom's argument proves Appellees' point: The only alleged inventive concept upon which Sequenom relies *is the non-patentable detection of a natural phenomenon itself*—the presence of cffDNA in maternal serum or plasma. The '540 patent claims simply instruct others to make more copies of cffDNA found in a maternal serum or plasma sample and then detect the cffDNA found in that sample—with no limitations of any kind (let alone inventive ones) on the amplification method or the detection method. Decades of Supreme Court precedent make clear that something more is required (*i.e.*, an "inventive concept")

to ensure that a patent claim contains meaningful limitations beyond the natural phenomenon itself.[11]

Sequenom obliquely refers to the "many marked differences between the '540 patent and the prior art the District Court cited," including "who is being tested (cancer patients of all genders and ages vs. pregnant women) and to what is being detected (tumor vs. fetal characteristics)." Br. at 53. But this statement again fails to appreciate that the "inventive concept" requirement must be analyzed *apart* from the natural phenomenon recited in the claim. *Mayo*, 132 S. Ct. at 1299 (other steps "were all 'well known,' to the point where, putting the formula to the side, there was no 'inventive concept' in the claimed application of the formula") (quoting *Flook*, 437 U.S. at 594). The only difference between the cited examples and the '540 patent claims is the *type* of cell-free DNA that is amplified and detected in plasma or serum. Simply pointing to "who is being tested" and "what is being detected" fails to identify the requisite "other inventive concept."[12] The claims of the '540 patent

[11] The "paternally inherited" limitation is not an inventive concept separate and apart from the natural phenomenon of cffDNA. Rather, it is a particular *characteristic* of the natural phenomenon that the inventors detected. The determination of whether a claim recites an inventive concept is done without reference to the natural phenomenon recited in the claim. *See supra* at Section II.

[12] BIO offers a parade of horribles that will befall the field of medical research if methods of detecting the "genetic basis for disease" are not patentable. *E.g.*, BIO Br. at 4-6. But the District Court did not go beyond the Supreme Court's precedent and declare that *all* such methods are not patentable. To the contrary, the court noted that "had the inventors of the '540 patent created an innovative method of

amount to nothing more than an instruction to find the natural phenomenon of cell-free fetal DNA in the cell-free portion of blood through well-known means—which were used previously to detect other types of cell-free DNA in the exact same place.

Diehr does not require a different outcome. Rather, in the language on which Sequenom relies, *Diehr* merely noted that "[i]t is inappropriate to dissect the claims into old and new elements *and then to ignore the presence of the old elements in the analysis*." *Diehr*, 450 U.S. at 188. Here, the District Court did not ignore any elements; it considered *each* element separately and in combination to determine that the claimed steps do not recite patent-eligible subject matter. Moreover, unlike the '540 patent claims, the *Diehr* claims did not simply append the steps of a conventional method to a natural phenomenon; they involved *new* steps reciting *different* actions, *e.g.*, "constantly measuring the actual temperature," as opposed to the conventional method of only measuring the temperature at one point. *Diehr*, 450 U.S. at 178. Thus, in *Mayo*, the Supreme Court noted that *Diehr* "nowhere suggested

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performing DNA detection while searching for paternally inherited cffDNA, such as a new method of amplification or fractionation, those claims would be patentable." A0017 (17:5-7). Each method that BIO fears would be patent ineligible must be analyzed on its own merits. Moreover, the Supreme Court recently warned against departing from its precedent "lest a new protective rule that seems to suit the needs of one field produce unforeseen results in another." *Mayo*, 132 S. Ct. at 1305. Accordingly, the '540 patent must be examined under existing precedent and, as in *Mayo*, this Court "need not determine here whether, from a policy perspective, increased protection for discoveries of diagnostics laws of nature is desirable." *Id*.

that all the[] steps, or at least the combination of those steps, were in context obvious, already in use, or purely conventional." 132 S. Ct. at 1299.

V. The Supreme Court's Decision in *Myriad* Supports the District Court's Conclusion

Nothing in *Myriad* supports Sequenom's position that its discovery of cffDNA in maternal serum or plasma, combined with pedestrian limitations encompassing well-known methods of amplifying and detecting that DNA, amounts to patent-eligible subject matter. Sequenom's argument—made for the first time on appeal—that increasing the amount of cffDNA by making copies is equivalent to the laboratory-created cDNA found patentable in *Myriad* fundamentally misconstrues the import of the Supreme Court's decision. Moreover, although *Myriad* did not involve method claims, it offered guidance on what would constitute a patent-eligible method that is directly applicable here.

A. *Myriad* Makes Clear that the Process of Isolating Newly Discovered Genetic Material through Conventional Means Is Not Patent-Eligible Subject Matter

In *Myriad*, the Supreme Court found that isolated sequences of the BRCA1 and BRCA2 genes did not constitute patent-eligible subject matter. *Myriad*, 133 S. Ct. at 2111. Although no method claims were at issue in *Myriad*, the Supreme Court noted that:

> Had Myriad created an innovative method of manipulating genes while searching for the BRCA1 and BRCA2 genes, it could possibly have sought a method

> patent. But the processes used by Myriad to isolate DNA were well understood by geneticists at the time of Myriad's patents[,] ... widely used, and fairly uniform insofar as any scientist engaged in the search for a gene would likely have utilized a similar approach....

133 S. Ct. at 2119-20 (internal quotation marks omitted). The Court's "had Myriad created" language is mirrored in the District Court's conclusion here that "had the inventors of the '540 patent created an innovative method of performing DNA detection while searching for paternally inherited cffDNA, such as a new method of amplification or fractionation, those claims would be patentable." A0017 (17:5-7). As with the inventors in *Myriad*, however, Drs. Lo and Wainscoat did not do so. *Myriad* thus reinforces the teaching of *Mayo* and previous Supreme Court decisions that the discovery of a natural phenomenon, such as genetic material, cannot be transformed into patent-eligible subject matter by appending processes "widely used, and fairly uniform insofar as any scientist engaged in the search for a gene would likely have utilized a similar approach …." *Myriad*, 133 S. Ct. at 2119-20.[13]

[13] Many of the arguments BIO makes in support of Sequenom are recycled arguments that failed to persuade the Supreme Court in *Myriad*. *See e.g.*, Brief for Amicus Curiae The Biotechnology Industry Organization In Support Of Respondents, *Assoc. for Molecular Pathology, et al., v. Myriad Genetics, Inc. et al.*, Case No. 12-398, at 24-25 (S. Ct. Mar. 2013) ("A rule limiting patent eligibility to cDNA could cut off that research in its infancy.").

B. The Asserted Claims of the '540 Patent, Unlike the cDNA Claims in *Myriad*, Do Not Recite or Require the Creation of any Novel, Man-Made Genetic Material

To circumvent *Myriad's* conclusion that isolating BRCA1 and BRCA2 genes was not patentable, just as detecting cffDNA is not patentable, Sequenom argues that practicing its claimed method of *detection* has the effect of *creating* "DNA strands that differ from the natural phenomenon." Br. at 56. Through these gymnastics, Sequenom attempts to analogize to the patentable cDNA in *Myriad*. *Id*. at 56-57.

That attempt fails. In *Myriad,* the Court held that claims to cDNA can be patent eligible because "creation of a cDNA sequence from mRNA results in an exons-only molecule that is not naturally occurring" and "the lab technician unquestionably creates something new when cDNA is made." 133 S. Ct. at 2119. An exons-only cDNA is new because natural DNA also contains non-coding sequences called "introns." *Id*. at 2111. The Court recognized, however, that cDNA was not "new" on account of its *other* structural differences from naturally occurring molecules, *e.g.*, those arising from the substitution of the nucleotide base thymine in cDNA in place of uracil in the naturally occurring mRNA sequences. *Id*. In fact, *Myriad* acknowledged the limits of its decision with regard to cDNA, noting that even cDNA is not patent eligible "insofar as very short series of DNA may have no

intervening introns to remove when creating cDNA. In that situation, a short strand of cDNA may be indistinguishable from natural DNA." *Id*. at 2119.

The logic of *Myriad* with respect to patent-eligible cDNA does not apply here. Cell-free fetal DNA (like the non-patentable isolated DNA in *Myriad*) is naturally occurring. Unlike making exons-only cDNA, no one "creates something new" when amplifying (making copies of) and detecting cell-free fetal DNA in maternal plasma or serum. *Cf. id.* Sequenom's amplification of cffDNA is no more transformative of the copied cffDNA than Myriad's patent *ineligible* short strand of cDNA having "no intervening introns to remove." *Id.*

Unable to rely on *Myriad's* cDNA holding, Sequenom attempts to argue for the first time on appeal that cffDNA that has undergone the "amplifying" step "is physically and chemically distinct from naturally occurring cffDNA." Br. at 57. Sequenom has waived this argument by failing to present it to the District Court in the first instance. "It is well-settled that, absent exceptional circumstances, a party cannot raise on appeal legal issues not raised and considered in the trial forum." *Finch v. Hughes Aircraft Co.*, 926 F.2d 1574, 1576 (Fed. Cir. 1991). There is no legitimate excuse for Sequenom's failure to raise this argument before the District Court, as the case and purported "facts" on which Sequenom relies were easily discovered at the time of briefing in the District Court. *Delaware Valley Floral Grp., Inc. v. Shaw Rose Nets, LLC*, 597 F.3d 1374, 1381 n.3 (Fed. Cir. 2010) ("Because

Shaw failed to raise this argument below, it has been waived and we need not consider it here.").

In any event, this new argument does not change anything. None of the alleged structural differences between naturally occurring cffDNA and amplified cffDNA relates to, or is recited in, the claimed method of the '540 patent. If any such structural differences played a role in the claimed method, they would be recited in the '540 patent claims or at least the specification. They do not. The '540 patent does not claim a composition of matter; it claims a *method for detecting naturally occurring cffDNA*. And the "amplifying" step, which Sequenom claims is transformative, instead has a simple and singular purpose—making more copies of cffDNA to facilitate detection. It has nothing to do with changing the structure of that cffDNA, and thus any minor structural differences are irrelevant. *Myriad*, 133 S. Ct. at 2118. ("Myriad's claims are simply not expressed in terms of chemical composition, nor do they rely in any way on the chemical changes that result from the isolation of a particular section of DNA."). Moreover, Sequenom does not argue that the "amplifying" step changes the sequence of those portions of the cffDNA that are copied—and the construction of "amplifying" (increasing the amount by making copies) requires no such changes. Unlike the cDNA found to be patentable in

Myriad, the amplified cffDNA here, as defined by the claim, is simply a copy of the cffDNA found in nature.[14]

C. Sequenom Cannot Properly Analogize to Claim 21 of Myriad's Patent

The District Court properly rejected Sequenom's arguments regarding the "'unchallenged' method claims" mentioned in *Myriad*. A0017 (n.8). *Myriad* is clear that "[i]t is important to note what is *not* implicated by this decision ... there are no method claims before this Court." *Myriad*, 133 S. Ct. at 2119 (emphasis in original).

Nonetheless, Sequenom again stretches *Myriad* to the breaking point by arguing that claim 21 of Myriad's U.S. Patent No. 5,753,441—a claim that was not challenged in the District Court, not analyzed by the Federal Circuit, and not discussed by the Supreme Court—was "likely" patent eligible even though it applied allegedly conventional steps to the naturally occurring BRCA1 gene that the inventors had isolated. Br. at 59-60. Sequenom argues that, by analogy, the similarly conventional "combination of techniques described" in the '540 patent also should be patentable. Br. at 60.

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[14] Although Sequenom's amplification-related arguments are based on the use of PCR, Br. at 6-8, Sequenom never directs its arguments specifically to the patentability of dependent claim 2, which limits claim 1 to amplification by PCR. To the extent that the Court interprets Sequenom's arguments as applying to claim 2 (as well as claim 1), even though Sequenom never expressly addresses its arguments to claim 2 (and has thus waived its right to challenge the District Court's opinion on claim 2), those arguments are meritless for the reasons discussed above.

Sequenom creates this self-serving analogy out of whole cloth. The Supreme Court *did not address* claim 21 or offer any view on whether, if that claim had been challenged, it would have been found to cover patent-eligible subject matter. The Court's passing reference to "unchallenged claims" does not call out (expressly or impliedly) any particular claim from any Myriad patent. Nor did the Court suggest, as Sequenom argues, that all of Myriad's unchallenged claims cover patent-eligible subject matter. The Court simply noted that "*[m]any* of [Myriad's] unchallenged claims are limited to" new applications of knowledge about the BRCA1 and BRCA2 genes. *Myriad,* 133 S. Ct. at 2120 (emphasis added).

Moreover, *no court* has offered any opinion as to the patent eligibility of claim 21. The District Court did not address it and, at most, this Court referred to it as an example of claims to "applications" of "knowledge of the [BRCA gene] sequences." *See Association for Molecular Pathology v. United States PTO*, 689 F.3d 1303, 1349 (Fed. Cir. 2012). But this Court offered no discussion of whether or why that claim would satisfy the Section 101 criteria. In particular, no court has ever determined, as Sequenom suggests, that the steps in claim 21 apply "text-book conventional and routine laboratory work." Br. at 60. Nor did Sequenom present any evidence to the District Court to support that characterization of those steps (Sequenom improperly tries in the first instance on appeal to cobble together factual support by combining

various passages from the Alberts and Sambrook biology treatises). Appellees' Opp'n to Sequenom's Mtn. for Judicial Notice at 9 (Dkt. No. 44).

Nor do the Supreme Court or Federal Circuit decisions in *Myriad* support the proposition that "methods applying known laboratory techniques to a newly-discovered natural phenomenon ... are patent eligible." Br. at 58. That proposition is contrary to decades of Supreme Court precedent. It is an entirely different matter where, as in *Myriad*, a claim is directed to a new composition of matter that does not exist in nature *created* by a technician in a laboratory. But that is not this case: The applicants here did not *create* anything; they used conventional techniques to detect a natural phenomenon. A natural phenomenon detected by a routine method is not patentable subject matter.

VI. The Preemption Analysis Does Not Alter the Conclusion That the Claims of the '540 Patent Are Not Patentable

Sequenom spends much of its brief arguing that the claims of the '540 patent are valid because they allegedly do not wholly preempt all uses of cffDNA. Sequenom advances an incorrect standard that is directly contradicted by recent decisions of this Court and the Supreme Court, misapplies or misstates controlling precedent, and relies on three research articles that, in addition to being irrelevant, fail to demonstrate that the '540 patent claims do not risk preempting all "substantial practical applications" of cffDNA. *See Mayo*, 132 S. Ct. at 1301.

A. Sequenom's "Complete Preemption" Test for Analyzing Patentability Conflicts with Supreme Court and Federal Circuit Authority

Sequenom argues "that a patent recites ineligible subject matter ***only*** when it claims for itself, or preempts ***all other uses*** of, an abstract idea, law of nature, or natural phenomenon." Br. at 28 (emphasis added). Sequenom has it wrong: Complete preemption is not a bright-line test for patent eligibility. To the contrary, the test is whether a "patent in practice amounts to significantly more than a patent upon the natural law itself." *E.g.*, *Mayo*, 132 S. Ct. at 1294. It is in this context that the Supreme Court explained in *Mayo*:

> Our conclusion [with respect to patent eligibility] rests upon an examination of the particular claims before us in light of the Court's precedents …. They warn us against upholding patents that claim processes that too broadly preempt the use of a natural law. ***And they insist*** that a process that focuses upon the use of a natural law also contain other elements or a combination of elements, sometimes referred to as an "inventive concept," sufficient to ensure that the patent in practice amounts to significantly more than a patent upon the natural law itself.

Id. (internal citations omitted) (emphasis added). Therefore, while concerns about preemption are an important consideration—*i.e.*, courts are *warned against* "upholding patents that claim processes that too broadly preempt the use of a natural law"—Supreme Court precedents "*insist*" that the claimed processes contain an "inventive concept" apart from the recited natural law. Accordingly, the absence of

complete preemption provides no "bright-line test" for resolving the patentable subject matter inquiry. *See id.; see also CLS Bank*, 717 F.3d at 1284 ("[T]he fact that there is no easy bright-line test simply emphasizes the need for the PTO and the courts to apply the flexible analysis ... to the facts at hand.") (Lourie J., concurring).

Furthermore, Sequenom could not be more wrong in suggesting that "a method applying or using a natural phenomenon in a manner that does not preclude alternative methods in the same field is non-preemptive and, by definition, patent eligible under Section 101." Br. at 30. *Mayo* demonstrates why Sequenom is wrong. *Mayo* addressed concerns about preemption—for example, that the claims at issue "threaten to inhibit the development of more refined treatment recommendations"—*only after* determining that the claims did not contain an inventive concept. 132 S. Ct. at 1302. If Sequenom were correct, the analysis would have been entirely different: The Supreme Court would have considered whether the claims preempted all other uses of the natural law and, if not, allowed the claims. But the Court took a different approach: It determined that the claims added "nothing of significance to the natural laws themselves" and only then referenced preemption to reinforce its conclusion of invalidity. *Id.*[15]

[15] In *Mayo*, the Court observed that "upholding the patents would risk disproportionately tying up the use of the underlying natural laws, inhibiting their use in the making of further discoveries." *Id.* at 1294. It is the "risk" of "disproportionately tying up the use of" a natural phenomenon through the lack of

It is certainly true that patents have been found invalid for wholly preempting a formula or abstract idea. *See Gottschalk v. Benson*, 409 U.S. 63, 71-72 (1972). But the *converse* is not true—the absence of complete preemption does not mean that a claim recites patentable subject matter. *See, e.g.*, *Mayo*, 132 S. Ct. at 1302.[16] As this Court recently observed, "even if a claim does not wholly pre-empt an abstract idea, it still will not be limited meaningfully if it contains only insignificant or token pre- or post-solution activity …." *Ultramercial, Inc. v. Hulu, LLC,* 722 F.3d 1335, 1346 (Fed. Cir. 2013) (citing *Mayo*, 132 S. Ct. at 1297-98).

B. Sequenom's Arguments to Defend its Erroneous Standard Misapply or Misstate Decisions of this Court and the Supreme Court

Sequenom takes great liberty with the established precedent to try to support its overreaching argument that preemption is *the* dispositive factor for patent eligibility.

For example, Sequenom attempts to frame this Court's several opinions in *CLS Bank* as supporting the notion that claims are patent eligible whenever they do

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inventive concept—not the actual complete preemption of a natural phenomenon—to which the patentable subject matter inquiry is addressed.

[16] Indeed, there are circumstances in which a preemption analysis has played no role in the patent eligibility analysis. For example, in *Funk Brothers*, the Supreme Court did not consider whether the claimed use for the combination of naturally occurring bacteria completely preempted all practical applications of it. Instead, the Court focused on the lack of an inventive concept separate and apart from the natural phenomenon. 333 U.S. at 131-32.

not wholly preempt the use of a natural phenomenon. *CLS Bank* says no such thing. Although Judge Lourie noted that it "is an abiding concern that patents should not be allowed to preempt the *fundamental tools of discovery*" and that "[g]uarding against the wholesale preemption of *fundamental principles* should be our primary aim in applying the common law exceptions to § 101," 717 F.3d at 1280-81 (emphasis added), those statements reflect uncontroversial building blocks of patent eligibility analysis: Each party to this appeal agrees that "fundamental discoveries" such as "laws of nature, natural phenomena, and abstract ideas" are not patentable. *Id*. at 1277.

Notably absent from Sequenom's brief is the very next paragraph in Judge Lourie's opinion, which begins: "To be clear, the proper focus *is not preemption per se*, for some measure of preemption is intrinsic in the statutory right granted with every patent to exclude competitors, for a limited time, from practicing the claimed invention." *Id*. at 1281 (emphasis added). Judge Lourie continued:

> Rather, the animating concern is that claims should not be coextensive with a natural law, natural phenomenon, or abstract idea; a patent-eligible claim must include one or more substantive limitations that, in the words of the Supreme Court, add "significantly more" to the basic principle, with the result that the claim covers significantly *less*.

Id. (citing *Mayo*, 132 S. Ct. at 1294) (emphasis in original). Judge Lourie thus articulated that the "abiding concern" regarding preemption is the *danger* that a

claim might "subsume the full scope of a fundamental concept," and thus "when those concerns arise, we must look for meaningful limitations that prevent the claim as a whole from covering the concept's every practical application." *Id*. (citing *Mayo*, 132 S. Ct. at 1302). Therefore, while preemption is certainly an important concern, it is not a one-stop determinative standard by which to judge patent-eligibility. Rather, where (as here) a claimed method implicates a natural phenomenon, courts "*must look for meaningful limitations* that prevent the claim as a whole from covering the concept's every practical application." *Id*. (emphasis added).

Moreover, nothing in *CLS Bank* supports the logical leap that Sequenom asks this Court to take, *i.e*., to conclude that a "non-preemptive" method is "*by definition*, patent eligible under Section 101." Br. at 30 (emphasis added). Judge Lourie disavowed this *per se* approach and Chief Judge Rader succinctly rejected it: "[E]ven if a claim does not wholly pre-empt an abstract idea, it still will not be limited meaningfully if it contains only insignificant or token pre- or post-solution activity …." *CLS Bank*, 717 F.3d at 1300.[17]

[17] Sequenom mischaracterizes Chief Judge Rader's opinion when claiming he stated that "a patent-eligibility problem *arises only* 'when a claim preempts all practical uses.'" Br. at 26 (emphasis added). Rather, Judge Rader stated that "*[p]re-emption is only a subject matter eligibility problem* when a claim preempts all practical uses of an abstract idea." *CLS Bank*, 717 F.3d at 1300. There is a significant difference.

To buttress its argument that preemption is the dispositive test, Sequenom accuses the District Court of mischaracterizing *Flook* and *Bilski* as "cases invalidating a *non*-preemptive patent" and thus "devalu[ing] preemption as a Section 101 analytical tool." Br. at 30. Sequenom misreads these cases. In *Flook*, the Supreme Court reiterated the prohibition against wholly preempting natural laws. 437 U.S. at 589. However, the Court then stated that "Respondent *correctly* points out that [the preemption prohibition] does not apply to his claims. He *does not* seek to 'wholly preempt the mathematical formula,' since there are uses of his formula outside the petrochemical and oil-refining industries that remain in the public domain." *Id*. at 589-90 (emphasis added). Instead, respondent/patentee argued that "the presence of specific 'post-solution' activity" made his process patentable. *Id*. at 590.

It was this latter argument—that the claims had been meaningfully limited—that the Court rejected. *Id*. Indeed, it was not the patentee's preemption argument that the Court declared "exalts form over substance," as Sequenom claims, Br. at 30, but "[t]he notion that post-solution activity, no matter how conventional or obvious in itself, can transform an unpatentable principle into a patentable process." *Id.* at 590. The Court in *Flook*, therefore, invalidated the claims for lack of inventive concept without engaging in a determinative preemption analysis. *Id*. at 594

(holding that the patentee's application of the natural law contained "no claim of patentable invention" because its components were "well known").

Sequenom also misstates *Bilski*, where the Court found that independent claim 1 was a non-patentable abstract idea that would preempt risk hedging in all fields. *Bilski v. Kappos*, 130 S. Ct. 3218, 3231 (2010). But, as the District Court noted, *Bilski's* approach to the *dependent* claims—which Sequenom ignores—illustrates that the *absence of complete preemption* does not mean that a claim recites patentable subject matter. A0018 (n.9). The dependent claims in *Bilski* did not wholly preempt the abstract idea because they were specifically directed to commodities and energy markets. *Bilski*, 130 S. Ct. at 3231. Nonetheless, the Court found those claims invalid because they added "less to the underlying abstract principle than the invention in *Flook* did" and "*Flook* established that limiting an abstract idea to one field of use or adding token postsolution components [does] not make the concept patentable." *Id*.

C. The Alleged "Three Non-Preemptive Alternative Methods" Do Not Make the '540 Patent Claims Patentable

Central to Sequenom's appeal is the premise that "three peer-approved, practical, alternative methods using cffDNA in maternal blood, none of which infringes the '540 patent," salvage the patentability of its claims. Br. at 36. Sequenom is wrong. The articles are irrelevant because the patent eligibility determination must be made as of the patent's priority date and the articles post-date

issuance of the patent. However, even if the articles were relevant to the patent-eligibility determination, all of them fail to identify a "substantial practical application" of cffDNA outside the scope of the asserted claims.

1. The Articles Are Irrelevant Because the Determination of Patent Eligibility is Made as of the Patent's Priority Date, Not Based on Post-Priority Developments in the Field

The District Court properly concluded that "Sequenom has failed to show that any alternative methods [of using cffDNA] existed at the time of the invention or at the time of issuance of the patent." A0019 (19:24-26). This conclusion reflects the unremarkable proposition that, like all other validity issues (such as anticipation, obviousness, written description, enablement, and indefiniteness), the determination of whether patent claims recite patent-eligible subject matter must be made as of the relevant priority date, not based on later developments in the field. *See* A3544. The articles cited by Sequenom were published in 2002, 2003, and 2012—all of which fall after the date of the earliest application to which the '540 patent claims priority (March 4, 1997), as well as the actual issuance date of the patent (July 10, 2001). The articles are thus irrelevant to the resolution of the patent eligibility question.

Under *Mayo*, it is the language of the claims that determines whether they are drawn to patent-eligible subject matter. *Mayo*, 132 S. Ct. at 1294-98. Accordingly, the District Court correctly analyzed whether the claims of the '540 patent were patent eligible as a matter of law when they issued. *See* A0019 (19:26-27) (noting

that the "effect of issuing the '540 patent was to wholly preempt all known methods of detecting cffDNA *at that time*") (emphasis added). This analysis was consistent with the notion that patents should not "tie up too much future use of laws of nature," *e.g.*, *Mayo*, 132 S. Ct. at 1302, because the effect of the patent on such "future use" must be judged from the beginning of the patentee's monopoly. That is when patent eligibility is analyzed, not years after patent issuance.

This Court made clear in *Ultramercial* that "any inquiry into the scope of preemption—how much of the field is 'tied up' by the claim—***by definition will involve historic facts***: identifying the 'field,' the available alternatives, and preemptive impact of the claims in that field." 722 F.3d at 1339 (emphasis added) (internal quotation marks omitted). This is consistent with the Supreme Court's analysis of the "inventive concept" requirement, as that requirement cannot be satisfied by "well-understood, routine, conventional activity ***previously engaged in by scientists who work in the field*.** Purely conventional or obvious ***[pre]-solution activity*** is normally not sufficient to transform an unpatentable law of nature into a patent-eligible application of such a law." *Mayo*, 132 S. Ct. at 1298 (quoting *Flook*, 437 U.S. at 590) (emphasis added) (internal quotation marks omitted); *see also Ultramercial*, 722 F.3d at 1339 (patent eligibility determination looks at whether claim limitations "were not ***at the time of filing*** 'routine, well-understood, or conventional'") (emphasis added).

To hold otherwise would make the patent-eligibility analysis dependent on the timing of the challenge and the ever-shifting factual landscape concerning developments in the relevant field; the outcome of that analysis with respect to a given patent could change from year to year depending on whether an alternative use was published or put into practical use in the interim. Such a result would transform the relevant inquiry from a question of law into an intensive factual determination that could morph over time, thus subjecting similar patents to different tests and injecting uncertainity into the analysis. That is not the law. The Supreme Court has placed the focus of the patent-eligibility inquiry on the claim language itself, not on the fortuitous existence (or absence) of alternative methods as of the time of that inquiry. *E.g*. *Mayo*, 132 S. Ct. at 1296.

2. Even if Considered for the Patent-Eligibility Analysis, the Articles Fail to Disclose a "Substantial Practical Application" of cffDNA Beyond the Claimed Method

The District Court concluded that none of the three articles disclosed *practical* alternatives to the asserted claims. A0019 (19:5-7). That analysis was correct. *Mayo, 132* S. Ct. at 1301 (claimed method must not preempt all "substantial practical application[s]" of the natural phenomenon); *see also Benson*, 409 U.S. at 71-72.

First, the article by Dr. Farideh Bischoff describes a *potential* method for sample collection from dried whole blood spots, as opposed to serum or plasma. *See*

A1215 (20:9-14). The article states that "*[i]f* continued work *also finds* high levels of fetal DNA in dried blood spots, *it is possible* that the dried spot method is better due to absence of anticoagulant." A0340 (emphasis added). But Sequenom offers no evidence that anyone ever actually used dried blood spots as a practical alternative to testing for cell-free fetal DNA in plasma or serum.[18]

Second, the article by van den Oever *et al*., describes a *hypothesis* for the possible use of single molecule sequencing of cell-free fetal DNA from maternal plasma for trisomy 21 detection: "We hypothesize, therefore, that this method might be more suitable for early noninvasive aneuploidy detection." A0348. The authors state that their method was not sufficiently tested to be practical, noting that "[b]efore the implementation of noninvasive trisomy detection into routine diagnostics several QC criteria must be determined and validated." *Id.* Sequenom

[18] The academic articles cited by Sequenom are replete with indicators of impracticability and uncertainty. For example, the Bischoff *et al*. article reports results on whole blood, which includes both cellular and cell-free DNA from the mother and fetus. In maternal whole blood, the maternal DNA is in vast excess to fetal DNA; the article reports fetal/maternal DNA ratios of 1:100 to 1:10,000. A0339-40. The high maternal DNA background severely complicates any use of whole blood for detection of relatively rare fetal DNA; in contrast, the '540 patent reports a significantly higher cffDNA/maternal DNA ratio for maternal serum. A0046 (16:22-23). Furthermore, the article provides no confirmation regarding the proportion of cffDNA preserved rather than degraded as a result of its methods. The high maternal DNA background and these uncertainties are likely among the reasons the method of Bischoff *et al*. was never developed into a practical alternative to using cffDNA from maternal plasma and serum.

offers no evidence that anyone has ever actually used this technology for any practical application.[19]

Finally, the article by Poon *et al.* describes *possible* methods for identifying cell-free fetal DNA by looking for fetal markers without distinguishing between paternally and maternally inherited DNA. *See* A1216 (21:1-6, n.5); A0359. The article states: "We explore the *possibility* of using epigenetic markers for the specific detection of fetal DNA in maternal plasma." *Id.* (emphasis added). The article further clarifies that any practical application of this use would depend on future developments which would provide "a clinically relevant panel of fetal epigenetic markers that can be used in a synergistic manner with conventional genetic markers in maternal plasma." A0365. Sequenom offers no evidence that anyone has ever used this method for any practical application.

Because Sequenom failed to present evidence of any other "substantial practical application" of cffDNA, *Mayo*, 132 S. Ct. at 1301, the District Court was correct to conclude that "the claims at issue pose a substantial risk of preempting the natural phenomenon of paternally inherited cffDNA," a finding that *supported* its

[19] The only company that ever sold the single molecule sequencing technology described in the article (Helicos Biosciences Corporation) went bankrupt because its sequencing machines were a commercial failure. *See, e.g.*, A1245-46. Moreover, the Helicos sequencer was not even available until more than a decade after the '540 patent was filed. *Id.*

prior conclusion that the "claims are not drawn to patent-eligible subject matter." A0019 (19:27-20:2).

Finally, Sequenom latches on to the District Court's use of the words "commercially viable" and attempts to convert "commercially viable" to "commercially successful."[20] *E.g.*, Br. at 42-44. The District Court did not apply the standard about which Sequenom complains. Rather, the District Court merely rejected Sequenom's contention that "substantial practical application" means only that the method "can be practiced." A0019 (19:5-21). Indeed, it makes sense that a *substantial practical* application of cffDNA must do more than be practiced in a laboratory, for example, or merely be "possible," as were the three examples cited by Sequenom. To conclude otherwise would read the words "substantial practical application" out of the Supreme Court's jurisprudence.

[20] In *CLS Bank*, Chief Judge Rader noted that the question of "whether the claim covers every practical application" of the abstract idea must "recognize that the Patent Act does not halt or impede academic research, without commercial ends, to test, confirm, or improve a patented invention." *CLS Bank*, 717 F.3d at 1300 n.3. Thus, even if the three "alternative methods" Sequenom cites were part of the relevant inquiry, their lack of practicability and their research-focus significantly reduce their weight in the patent-eligibility analysis. This is particularly true of the Poon, *et al*, article, on which Dr. Lo—an inventor on the '540 patent—is a named author. Dr. Lo's continued *research* in the field in no way suggests that his earlier work has not risked foreclosing all *practical* applications of his original discovery.

CONCLUSION

For the reasons set forth herein and the accompanying record, this Court should affirm the District Court's October 30, 2013 Order granting Ariosa's motion for summary judgment on the grounds that the claims of the '540 patent are not directed to patentable subject matter.

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CERTIFICATE OF SERVICE

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CERTIFICATE OF COMPLIANCE WITH RULE 32(a)

1. This brief complies with the type-volume limitation of Federal Rule of Appellate Procedure 32(a)(7)(B). The brief contains 13,906 words, excluding the parts of the brief exempted by Federal Rule of Appellate Procedure 32(a)(7)(B)(iii) and Federal Circuit Rule 32(b).

2. This brief complies with the typeface requirements of Federal Rule of Appellate Procedure 32(a)(5) and the type style requirements of Federal Rule of Appellate Procedure 32(a)(6). The brief has been prepared in a proportionally spaced typeface using Microsoft Word 2010 in 14-point Times New Roman font.

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